REMARKS/ARGUMENTS

I. Status of the Claims

Claims 1, 6, 8, 10-24, 26, 27, 30, 33, 34-42 are pending in this application. Claims 16-23 are withdrawn from consideration. Claim 38 is cancelled. Claims 1, 6, 8, 10-15, 24, 26, 27, 30, and 33-42 are currently under consideration. Claims 1 and 6 are amended to add the term "substituted or unsubstituted". Support is found in claim 5 as filed. Claim 37 is amended to recite CDR1 and CDR3 sequences of the antibody in the claims. Support is found at least in Figure 1 of the application as filed. Claim 43 is new. Support can be found throughout the specification, for example 2 and in figures 2 and 4. Applicants respectfully request entry of the claims as amended.

Applicants appreciate the withdrawal of the rejections under 35 USC 112, first and second paragraph.

New Rejections/Objections

II. Response to Claim Rejections/Objections

Claim Objections

Claims 6, 8 and 40-42 are objected to for allegedly failing to further limit the subject matter of a previous claim. In response Applicants note that claim 1 has been amended for clarity to specify that the "macrocyclic metal chelate is substituted or unsubstituted...(DOTA)". Thus, the claim is not limited to a specific compound. Rather, the macrocyclic metal chelate is substituted or unsubstituted. Claims 6, 8 and 40-42 further define this metal chelate. Applicants respectfully request the Examiner to withdraw this objection.

Rejection under 35 U.S.C. 112, Second Paragraph

Claim 37 is rejected under 35 U.S.C. 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Particularly, the Examiner states that it is

> unclear whether the antibody of claim 1 further includes the sequences defined in claim 37 or whether both sequences define 1) the antigen recognition domain that recognizes a macrocyclic metal chelate, 2) the targeting moiety that binds to a tumor associated of [*sic*] 3) define the antigen recognition domains individually.

For the sake of expedient examination, and without acquiescing to this ground for rejection, claim 37 has been amended to recite that the "antigen recognition domain of said antibody" comprises the recited sequences. In view of the amendment to the claim, Applicants request withdrawal of this rejection.

Rejection under 35 U.S.C. 112, First Paragraph

Claims 1, 6, 8, 10-15, 24, 26-27, 30 and 33-42 are rejected as allegedly lacking written description under 35 U.S.C. 112, first paragraph. The Examiner noted that the claims include a genus of bispecific antibodies comprising an antigen recognition domain and a targeting moiety and that claim 1 and 37 broadly encompass antibodies having variations within the 6 CDR regions but are still capable of binding to a macrocyclic metal chelate and a tumor associated antigen. However, according to the Examiner, the written description only sets forth an isolated antibody or fragment thereof comprising sequences 100% identical to SEQ ID NO:1 and 5, wherein one arm of the antibody binds to a tumor antigen and a second arm binds to a tumor associated antigen or a macrocyclic metal chelate. Applicants respectfully traverse the rejection.

The analysis of whether a specification complies with the written description requirement calls for the Examiner to compare the scope of the claim with the scope of the description to determine whether applicant has demonstrated possession of the claimed invention. Such a review is conducted from the standpoint of one of skill in the art at the time the application was filed and should include a determination of the field of the invention and the level of skill and knowledge in the art. *See, e.g.*, Wang Labs. v. Toshiba Corp., 993 F.2d 858, 865 (Fed. Cir. 1993). Information which is well known in the art need not be described in detail in the specification. *See, e.g.*, Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1379-80 (Fed. Cir. 1986).

The instant specification provides adequate written description for the pending claims. The Examiner appears to have focused the rejection on the description of the antigen recognition domain and alleges that the specification fails to provide a written description for anything other than the sequences of SEQ ID NO:1 or SEQ ID NO: 5.

Applicants note that claim 1 is directed to a method that requires the use of an antibody comprising an antigen recognition domain. This antigen recognition domain recognizes a macrocyclic metal chelate, this macrocyclic metal chelate comprises substituted or unsubstituted 1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid (DOTA), and comprises a reactive functional group with a reactivity complementary to said antibody reactive site. The antigen recognition domain also comprises a reactive site within the structure of the antibody that is not present in the wildtype of the antibody, wherein the reactive site is in a position within the antigen recognition domain. Thus, in

contrast to the Examiner's characterization, the antigen recognition is defined functionally and requires more than simply binding to a macrocyclic metal chelate.

Looking to the specification, Applicants note that the specification provides the sequences of multiple heavy chains and light chains that bind DOTA. Specifically, Figures 2 and 4 provide the sequence of the variant heavy and light chain polypeptides, respectively. In addition, paragraphs 103, 113 and 114 provide further written descriptions of the variant antibodies. As such, Applicants submit that the specification in fact, does provide an adequate written description of the subject matter of claim 1.

The Examiner also suggested that the specification did not provide a written description of the subject matter of claim 37, which recited that the antibody had a first sequence at least 95% sequence identity with SEQ ID NO: 1 and a second sequence having 95% identity with SEQ ID NO: 5. Again, Applicants respectfully disagree. As demonstrated above, the specification provides antibody heavy and light chains with different sequences. As such, the written description requirement for claim 37 should be satisfied. In addition, Applicants note that claim 37 has been amended to recite that the antibody has 95% identity to SEQ ID NO: 1 and also comprises CDR1 having the amino acid sequence of SEQ ID NO:2 and CDR3 having the sequence of SEQ ID NO:4; and wherein said antibody has a second sequence having at least 95 % sequence identity with SEQ ID NO. 5, and also comprises CDR1 having the amino acid sequence of SEQ ID NO:6 and CDR3 having the sequence of SEQ ID NO:8. Applicants submit that the written description for this claim is clearly satisfied as demonstrated in figures 2 and 4 and paragraphs 103, 113 and 114. Applicants respectfully request the Examiner to withdraw the rejection.

Rejection under 35 U.S.C. 103(a)

Claims 1, 6, 8, 10-15, 24, 26-27, 30, 33-36 and 38-39 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al. (WO 99/66951) in view of Chmura et al. (PNAS 2001; **98**: 8480-8484).

As noted previously, to construct a *prima facie* case of obviousness, the cited references must meet three criteria. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all of the claim limitations. *In re Vaeck*, 947 F.2d 488, (Fed. Cir. 1991). As stated in the May 3, 2007 memorandum from Margaret A. Focarino to the USPTO Technology Center directors, these elements must still be considered, even under the Supreme Court ruling for KSR Int'l Co. v. Teleflex, Inc., (No. 04-1350 (U.S. Apr. 30, 2007)), and that "in formulating a rejection under 35 U.S.C. §103(a) based upon a combination of prior art elements, it

remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed." Applicants respectfully submit that each of the required criteria set forth above have not been satisfied and thus, a *prima facie* case of obviousness has not been set forth.

Hansen discloses bi-specific antibody conjugates. In some embodiments, Hansen indicates that one arm of the bi-specific antibody binds a hapten, which can include chelators. However, Applicants maintain that at best, Hansen mentions that DOTA may be useful in a list of potentially useful chelators (see p. 23 of Hansen). Accordingly, Applicants submit that there is no specific teaching that DOTA could be a direct target of an antibody in a bifunctional antibody conjugate. Moreover, while the Examiner has relied on Chmura to provide motivation to combine Hansen and Chmura, Applicants respectfully submit that this is in appropriate.

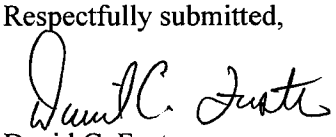
Hansen notes that the "arm of the bsAb that binds to the low MW hapten must bind with high affinity." (See p. 2 of Hansen) However, Hansen also notes the problems associated with this high affinity, namely that "[b]ecause the Abs were raised against the chelators and metal chelate complexes, they have remarkable specificity for the complex against which they were originally raised... This great specificity has proven to be a disadvantage in one respect, in that other nuclides...cannot be readily substituted into available reagents for alternative uses." However, the present claims are directed to methods that result in a marked increase in affinity, e.g. a covalent attachment, between the bi-functional antibody and the macrocyclic metal chelate. Applicants remind the Examiner that "It is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983)" see MPEP 2145 (X)(D)(2). The doctrine that "teaching away" supports a finding of non-obviousness is supported in the recent Supreme Court case, *KSR v. Telefax,* No. 04-1350, page 12, citing *United States v. Adams.* Thus, because Hansen cautions against antibodies that are too specific, Applicants submit that one of skill in the art would not have been motivated to produce an antibody for use in the method of Hansen wherein the antibody had a marked increase in affinity, e.g. a covalent attachment, between the antibody and the hapten. For at least these reasons, Applicants submit that the claims are not obvious. Applicants request that the Examiner withdraw the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-442-1000.

Respectfully submitted,



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